of the NEPHRIC trial \(n = 129\) patients, which shows a smaller incidence of contrast-induced nephropathy by using iso-osmolar contrast media [2]. However, we also have not changed our routine daily clinical approach in 2008 by using the low-osmolar contrast media, because the published results were conflicting in the last 2 years.

In our paper, we emphasized these conflicting results concerning the value of the osmolality of a contrast media (iso-osmolar versus low-osmolar) in preventing contrast-induced nephropathy by citing three recent trials (RECOVER with \(n = 300\) patients published in 2006, IMPACT with \(n = 166\) patients published in 2006 and CARE with \(n = 414\) patients published in 2007).

It was described by the authors of the RECOVER trial, Jo et al., that they indeed found a benefit regarding the composite end-point. Regarding the end-point defined by Aspelin et al. in the NEPHRIC trial, no benefit of the iso-osmolar contrast media could be demonstrated [3].

In the IMPACT and the CARE trial there were no different rates of contrast-induced nephropathy by the use of low- versus iso-osmolar contrast media [4,5]. The CARE trial is the most recent and largest, prospective, randomized double-blind trial comparing the iso-osmolar iodoxanol-370 with the low-osmolar iodixanol-320: when a composite end-point was assessed, the rate of contrast-induced nephropathy was not significantly different (10.3% versus 12.9%) after the administration of the different contrast media [5].

From our point of view, the results are so conflicting that there is no evidence of the superiority of the iso-osmolar versus the low-osmolar contrast media and no firm recommendation based on the overwhelming majority of evidences can be made.

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**S-cystatin C formulae or combination of s-cystatin C and s-creatinine formulae do not improve prediction of GFR**

Sir,

We read with great interest the original article by Tidman et al. [1] on the development and validation of the new Orebro-cyst formulae for GFR estimation based on cystatin C serum concentration and combination (mean) of the new formulae and the MDRD equation. The Orebro-cyst equations are constructed using the calculated production rate and extra-renal clearance of cystatin C. Two equations are formulated for different methods of cystatin C determination (DAKO and Gentian). In the aforementioned paper, a formula that combines MDRD and Orebro-cyst provided a greater accuracy than formulae based on s-creatinine or s-cystatin C alone. We have investigated whether the new Orebro-cyst (Gentian) equation or its combination with MDRD can improve proportion of correctly classified patients for CKD stages in our cohort.

Our study was performed on 100 Caucasian subjects: 57 CKD patients, 28 kidney transplant patients and 15 volunteers. In all cases GFR was measured as the plasma clearance of iohexol (iGFR). Creatinine was determined by an enzymatic method (Randox) and plasma clearance of iohexol (iGFR). Creatinine was determined by an enzymatic method (Randox) and cystatin C by PENIA (Dade Behring). The median (range) of the measured GFR was 22 (7–124) ml/min/1.73 m². The estimated GFR (eGFR) was calculated based on creatinine concentration by the Cockcroft–Gault formula corrected to body surface area (CG/BSA), the abbreviated MDRD equation (aMDRD) and Mayo Clinic quadratic equation, and based on cystatin C serum concentration by Hoek, Larsson and Orebro-cyst (Gentian) equations. The performance of these formulae was analysed according to recommendations in the NKF K/DOQI guidelines. Table 1 shows percentage of patients correctly classified for the different stages of CKD based on the calculated eGFR.

In our study group the most accurate results were obtained with the Mayo Clinic quadratic equation [2]. Results were within 30% of iGFR in 85% and within 50% of iGFR in 95% of the cases. The median (range) of eGFR was 19.50 (7–141) ml/min/1.73 m². The bias was 1.6 ml/min/1.73 m² and precision (±1.96 × standard deviation from difference) −16.6–19.8 ml/min/1.73 m². The Orebro-cyst formula was significantly less accurate than the Mayo Clinic equation. Results were within 30% of iGFR in 63% and within 50% of iGFR in 82% of the cases. The median (range) of eGFR was 18.00 (4–168) ml/min/1.73 m². The bias was 6.0 ml/min/1.73 m² and precision −24.2–36.1 ml/min/1.73 m².

The formula created by combination of the Orebro and aMDRD equation was more precise than Orebro or Mayo Clinic alone (−13.5–14.3 ml/min/1.73 m²) and less biased (0.4 ml/min/1.73 m²), but accuracy was not better than Mayo Clinic (within 30% of iGFR in 79% and within 50% of iGFR in 95% of the cases). The proportion of correctly
classified patients was not better than for the Mayo Clinic formula.

To our knowledge there is no previous report on evaluation of Orebro-cyst or combination of the Orebro-cyst and MDRD equation in independent patients group. Unlike Tidman et al., we could not show superiority of combination of both s-creatinine and s-cystatin C formulae for GFR estimation in our patients. In our opinion, none of the evaluated equation was suitable for GFR estimation in diverse population. All of them may cause misclassification in a selected group of patients.

Conflict of interest statement. The results presented in this paper have not been published previously in whole or part, except in abstract form.

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Reply

Sir,

We appreciate the comments made by Joanna Urbaniak et al. concerning our article [1] and their evaluation of our cystatin C formula for eGFR (Orebro-cyst). Although the methods we both have used for determining cystatin C (Gentian and Dade-Behring) have been shown to give similar results [2], the Orebro-cyst bias of 6 ml/min/1.73 m² reported by Urbaniak et al. is probably due to the difference in the methods. This problem will not be solved until an international calibrator for cystatin C becomes available.

eGFR from cystatin C and creatinine are associated with different sources of errors. Therefore, the combination of the two markers should give a better overall estimate, which both our studies indicate. The patient population used for deriving the eGFR formula is critical. The serum creatinine concentration at a particular GFR is different in different populations such as healthy, lean or obese adults, children, CKD, diabetes or transplanted patients. The MDRD formula was derived from CKD patients whereas the Mayo Clinic quadratic equation was from both healthy individuals and patients with CKD. A simple way to choose the right formula is to look at the patient, avoiding creatinine formulae for patients with an abnormal muscle mass and cystatin C formulae when the GFR is low. We do not use cystatin C when GFR is <15 ml/min/1.73 m² since we have found that the 95% confidence interval of eGFR of about ±(30–40%) increases sharply below GFR values <20 ml/min/1.73 m². Cystatin C is better than creatinine in detecting a slight decrease in renal function and in detecting rapid deterioration in renal function [3].

The subject material in the study of Urbaniak et al. is small, being composed of healthy volunteers, CKD and transplanted patients and was unevenly distributed. Median GFR was 22 ml/min/1.73 m², with 43 of the 100 patients in stage 5 (<15 ml/min/1.73 m²), where cystatin C in our opinion should not be used. In stages 1 and 2 each patient represents 9%. The bias of 6 ml/min/1.73 m² of the Orebro-cyst formula makes a large contribution to the low accuracy in stage 5 compared with the other stages. The distribution of stages in the subject material and the fact that cystatin C is a better marker at higher GFR levels may explain that Urbaniak et al. found less bias and higher accuracy for the creatinine-based Mayo Clinic quadratic equation than for the Orebro-cyst. The combination of aMDRD and Orebro-cyst showed less bias than the Mayo Clinic quadratic equation.

The advantage of our formula over other cystatin C formulae for estimating GFR is that Cys-pr and CL-nr can easily be calculated from relatively few patients [1,4] and thus the formula can be adapted to the local laboratory

Table 1. The proportion of correctly classified patients for CKD stages

<table>
<thead>
<tr>
<th>iGFR</th>
<th>n</th>
<th>CG/BSA (%)</th>
<th>aMDRD (%)</th>
<th>Mayo Clinic (%)</th>
<th>Hoek (%)</th>
<th>Larsson (%)</th>
<th>Orebro-cyst (%)</th>
<th>Mean aMDRD/Orebro (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>11</td>
<td>36</td>
<td>9</td>
<td>91</td>
<td>91</td>
<td>82</td>
<td>100</td>
<td>91</td>
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<tr>
<td>60–89</td>
<td>11</td>
<td>82</td>
<td>45</td>
<td>64</td>
<td>55</td>
<td>18</td>
<td>55</td>
<td>64</td>
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<tr>
<td>30–59</td>
<td>21</td>
<td>71</td>
<td>90</td>
<td>71</td>
<td>76</td>
<td>90</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>15–29</td>
<td>14</td>
<td>64</td>
<td>57</td>
<td>50</td>
<td>79</td>
<td>57</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>&lt;15</td>
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<td>86</td>
<td>93</td>
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<tr>
<td>Total</td>
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<td>64</td>
<td>70</td>
<td>79</td>
<td>55</td>
<td>63</td>
<td>75</td>
<td>78</td>
</tr>
</tbody>
</table>

iGFR—plasma iohexol clearance (ml/min/1.73 m²); n—number of patients.